ON THE VALUE OF QUINOIDINE PREPARATIONS IN MALARIA,

WITH SPECIAL REFERENCE TO "LAVERAIN."

BY

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IN the Malarial season of 1912 investigations were commenced into the efficacy of the Amorphous Alkaloids of Quinine in the treatment of Malaria, and the results obtained went to show that these substances are of greater value than the Sulphate and Hydrochloride of Quinine.

As is well-known, Cinchona bark contains alkaloids in varying proportions. The principal ones are Quinine, Cinchonidine, Quinidine and Cinchonine, all of which can be crystallised and obtained perfectly pure. Besides these, there are also Hydroquinine, Hydrocinchonidine, and so on, in which a vinyl group has been replaced by an ethyl group. From the first group the ordinary salts of Quinine—the Sulphate, Hydrochloride, &c., are manufactured.

After separating all these, a mixture of alkaloids is left which cannot be crystallised and from which no *crystalline* salts can be prepared.

This amorphous substance was first recognised by Seturner in 1830, and was named by him as Quinoidine.

It is quite different from the "Amorphous or Residual Alkaloid" which contains Quinine, Cinchonidine, Quinidine, &c., and only some 30% of Quinoidine.

It is supposed that the amorphous nature of the Quinoidine renders it more assimilable and possibly accounts for its greater efficacy.

My investigations into the relative value of the Quinine Salts went to show that the Sulphate of Quinine was more effectual than the Hydrochloride, and that forty-five to sixty grains of either salt were sufficient to bring any malarial temperature to normal. As explained in my article (I.M.G., March 1913) this is the only practical test that can be applied in ordinary hospital or out-patient practice. It is not possible to keep patients in bed for a long period after their fever has left them, nor as a general rule is it practicable to make *repeated* blood examinations to detect the persistence or absence of parasites.

Quinine Sulph.
" Hydroch.

Quinoidine tests. Now as to the action of Quinoidine.

This drug was (in 1912) tested by me in 62 cases. All of these were Malaria, *i.e.*, the malarial parasite was present in the blood before the drug was administered. Many of the patients had suffered for many days before treatment had commenced and they were all sufficiently ill to leave their work and seek admission to hospital. Moreover, Hughli, where these investigations were carried out is a highly malarious district where a little fever is lightly thought of, and where patients do not readily come to hospital for this disease.

Two groups of cases were made. To the first 27 cases two grains of Quinoidine thrice daily were given, to the second group of 35 cases four grains were given thrice daily.

Dosage.

The tablets were given with a drink of water, and in no special relation to meals—just as they happened to be due in the ordinary hospital routine. Particular care was always taken to commence treatment with a five grain dose of Calomel washed down by an ounce of White mixture or similar saline.

Of the first 27 cases 11 were Benign Tertian, 13 were Malignant Tertian, and 3 were Quartan.

Results. These 27 cases reacted as follows :—

Eleven *Benign Tertians* required an average quantity of 9 grains of Quinoidine to stop their fever and were given an average of 22·5 grains each in all.

Thirteen *Malignant Tertians* required an average quantity of 10·38 grains of Quinoidine to stop fever and were given an average of 21 grains each in all.

Three *Quartan* cases required an average of 22 grains of Quinoidine to stop fever, and were given an average of 29·3 grains each in all.

Average doses of Quinoidine required to stop fever in Malaria.

	Average quantity of Quinoidine to stop fever (per head).	Total average quantity of Quinoidine given to each patient.
I.—Quinoidine ... dose ii grains t. d. s.		
Benign Tertian cases ...	9 grains	22·5 grains.
Malignant Tertian cases ..	10·38 ,,	21 ,,
Quartan type cases ...	22 ,,	29·3 ,,
II.—Quinoidine ... dose ii grains t. d. s.		
Benign Tertian cases ...	13·8 ,,	37·2 grains
Malignant Tertian cases ...	16·6 ,,	46·8 ,,
Quartan type cases ..	24 ,,	48 ,,

Case Histories.

Cases treated with two grains thrice daily.

(Short History).

Table C.

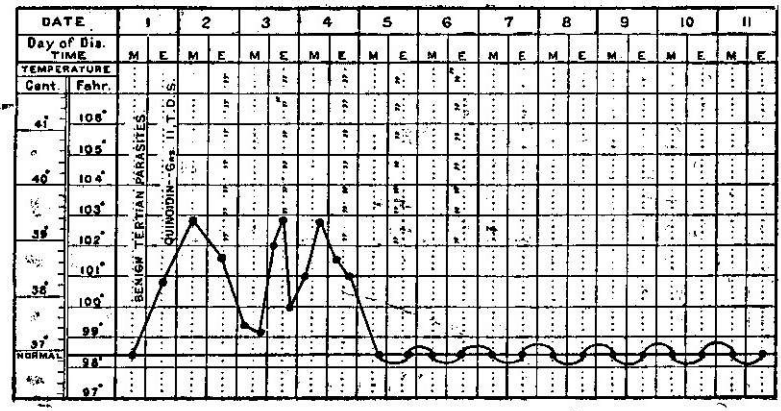


CHART I. Quinoidine.

Sew Dutt Tewari (Chart I) had suffered from fever for 4 or 5 days before admission to hospital. Parasites (B. T.) were present in his blood. Eighteen grains of Quinoidine brought the temperature to normal.

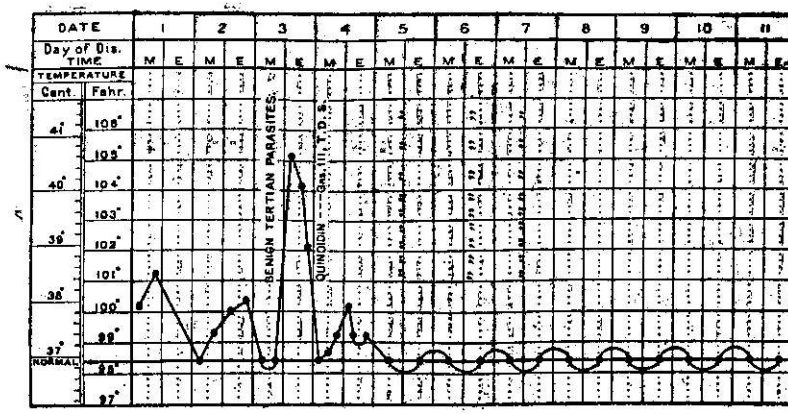


CHART II. Quinoidine.

Nister, female (Chart II), had fever for 8 days before admission to hospital. Parasites B. T. gametes were in the blood. Temperature rose to 105°. Six grains of Quinoidine stopped the fever. No relapse whilst in hospital.

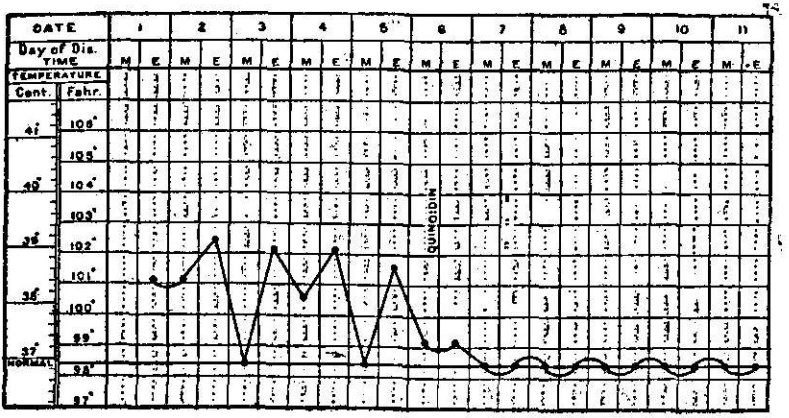


CHART III. Quinoidine.

G. H. Blake, European (Chart III), admitted with history of 5 days fever. Had vomiting and gastric catarrh. Liver much enlarged, tongue dry. Very ill. Had tramped about the country in search of work. M. T. parasite discovered on 4th day after admission. Six grains of Quinoidine stopped the fever. No relapse whilst in hospital.

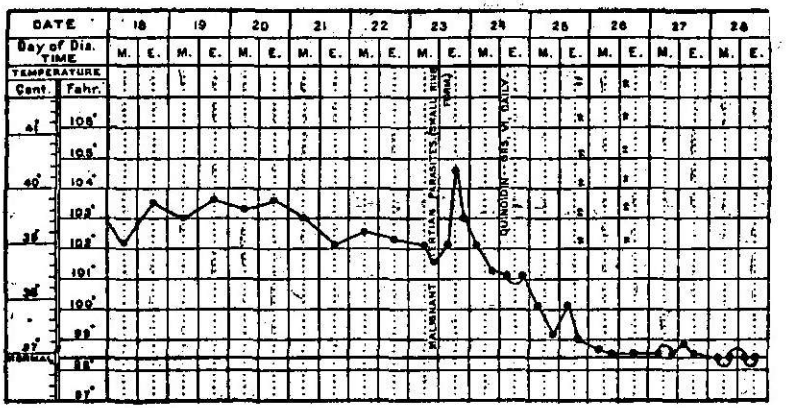


CHART IV. Quinoidine.

Topi Ram (Chart IV) had repeated attacks of fever for 21 days, and continuous fever for 11 days before admission. Spleen not enlarged. Low muttering delirium. Diarrhœa.

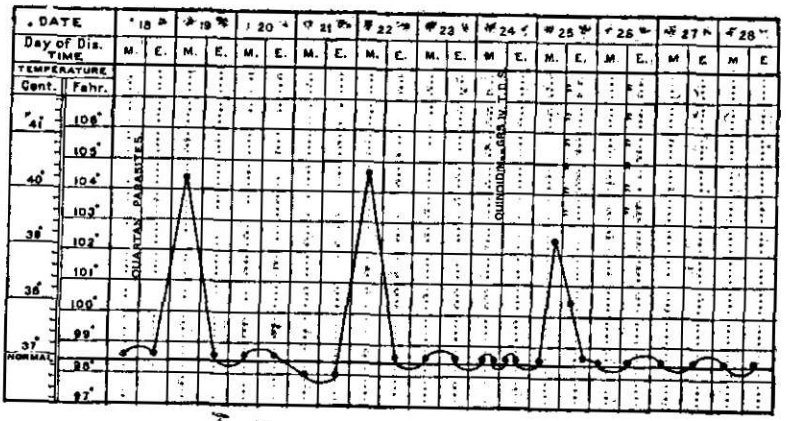


CHART V. Quinoidine.

Gobindo Doyal (Chart V). Repeated attacks of fever before admission. Spleen enlarged. Quartan parasite in the blood. Twelve grains of Quinoidine reduced the temperature to normal. No relapse whilst in hospital. This patient suffered from 'dysentery" after the fever and ascribed it to the medicine.

To the second series of 35 cases, Quinoidine in four grain doses was given, for in some of the two grain cases, it appeared that the smaller dose was not enough to control the fever.

In this series there were 20 Benign Tertian cases, 12 Malignant Tertian, and 3 Quartan.

The results were as follows :—

20 Benign Tertian cases required an average of 13½ grains to bring the temperature to normal.

12 Malignant Tertian cases required an average of 16½ grains to bring the temperature to normal.

3 Quartan cases required an average of 24 grains.

It thus appears at first sight that the larger doses were less effectual than the small ones but this I think is not really the case. The difference is not large and is probably accounted for by the drug being given in larger quantities in each day and so over-running the fever to some extent. The Benign Tertians required less than the Malignant Tertians, whilst the Quartans, true to their reputation, required considerably more than either.

Cases treated with xii grains daily of Quinoidine.

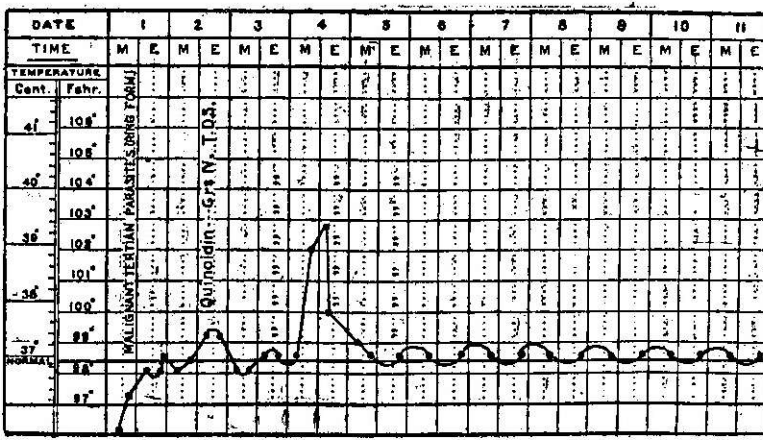


CHART VI. Quinoidine.

Ram Golash Roy (Chart VI) had been suffering from continuous fever for 3 or 4 days. On admission, collapsed with severe purging and vomiting. Pulse irregular and intermittent, much prostration. An excellent example of the pernicious or Algid type of malaria. This is the most interesting case of the series. The patient was dangerously ill on admission and apparently suffering from cholera, but the M. T. rings were found in the blood. On the day of admission the temperature was subnormal and the condition desperate; on the second day the temperature was still subnormal and the man very ill; on the third day Quinoidine, grains xii were given. There was an attack of fever in the evening, and though the man was very ill he was not quite so ill as on the first day. The temperature rose only to 99°. The next day there was no attack; the man was fairly well and the Quinoidine was continued. On the 5th, there was a sharp attack of fever in the afternoon, the temperature reaching 103°, but the patient said he felt much better, and his general appearance confirmed this. There was no prostration nor any of the typical pernicious signs, and after this the patient had no further attacks. It seems, therefore, that the improvement in the man's condition was definitely indicated by the rise of his temperature—a sign which is new to me and which I have not seen in the books.

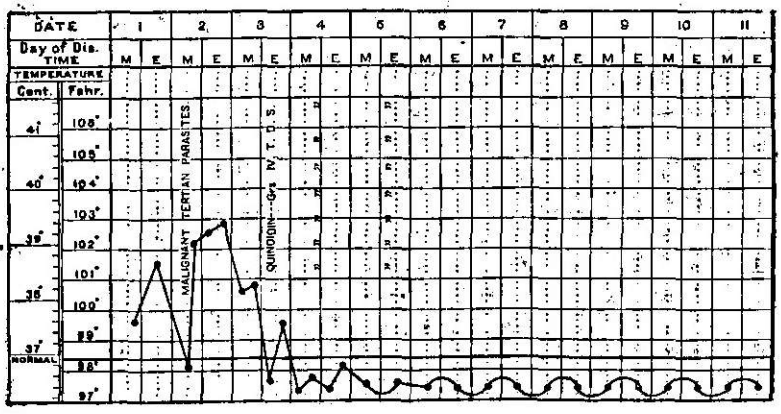


CHART VII. Quinoidine.

Kushem (23) (Chart VII).—The patient had been suffering from fever for 10 days before admission. The spleen was enlarged. Malignant Tertian parasites found. Quinoidine, grains iv t. d. s. were given and rapidly reduced the temperature to normal.

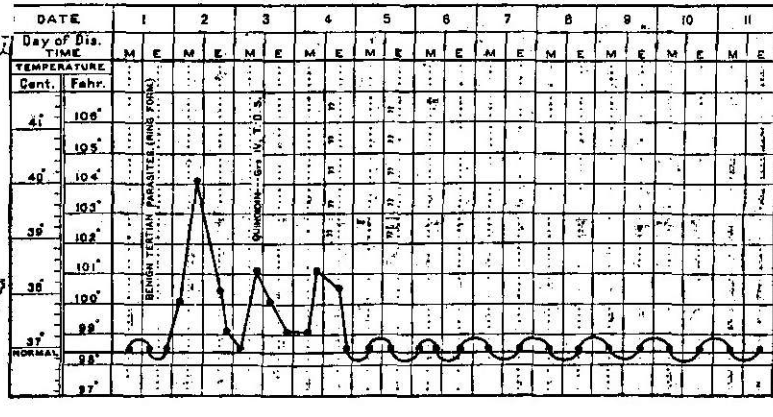


CHART VIII. Quinoidine.

(10) Sukhur Gwala (Chart VIII). Admitted on 17th September 1912. Had suffered from repeated attacks of fever for 3 weeks. His spleen was enlarged. Young Benign Tertian parasites in the blood. Quinoidine, grains iv, thrice daily—24 grains in all, aborted the next attack. Patient discharged cured on 22nd.

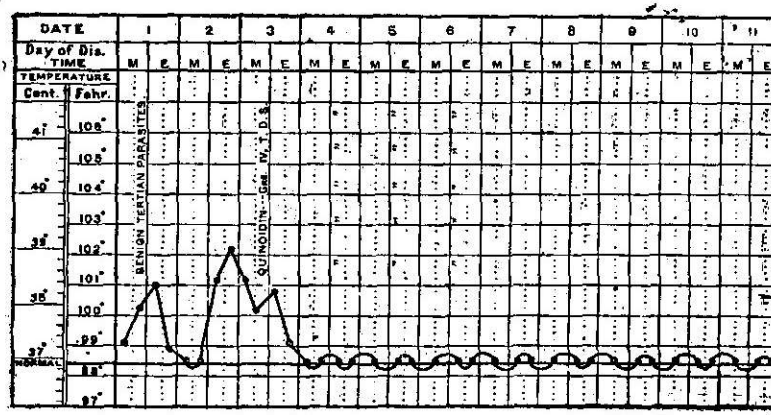


CHART IX. Quinoidine.

(9) Kali Kristo Banerji (Chart IX). Admitted on 2nd October 1912. Had suffered from repeated attacks of fever for four months, each attack lasting for eight or nine days. Spleen not enlarged, jaundice. Young Benign Tertian parasites in the blood. Quinoidine, grains iv, thrice daily., Twelve grains stopped the fever. No relapse whilst in hospital.

"Laverain." The action of Quinoidine Picrate "Laverain":—

The above investigation has been continued during the current year in my wards at the Medical College, Calcutta; but the plain Quinoidine has been modified by the addition of Ammonium Picrate grs. $\frac{1}{3}$ and Arsenious Acid gr. $\frac{1}{30}$ to each 2 grain tablet.

The Ammonium Picrate is efficacious in the treatment of Ague and Chronic Malaria, and is used, particularly for the latter purpose, in some intensely malarial districts.

The Arsenious Acid has been added for its general tonic effect and its stimulating effect on metabolism, particularly in chronic malaria.

I consider this combination to be distinctly preferable to the plain Quinoidine, for in addition to the specific action on the malarial parasite, the tonic action of the Arsenic and Picrate are also obtained. To this formula the name "Laverain" has been given, *vide I. M. Gazette*, July 1913.

The records for the current year are not yet complete, but following are brief notes and charts of cases treated with "Laverain" in my wards at the Medical College Hospital, Calcutta. In Calcutta it is difficult to insist on the presence of the Malarial parasite as an essential in all cases. Many patients have either been given some quinine in the outpatient department, or have taken it in small doses before seeking admission to hospital.

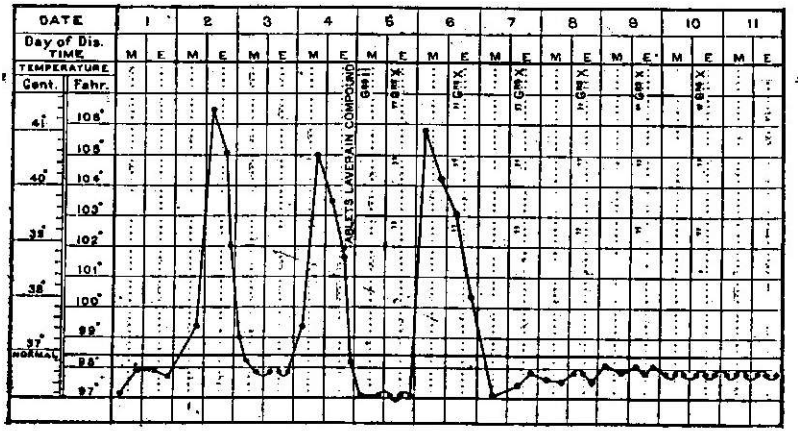


CHART I. "Laverain."

Case I.—Mrs. G., aged 18 years. (Chart I). Resident of Calcutta. Fever off and on for a month and a half. For the last 10 days coming every alternate day with rigor. Spleen slightly palpable and tender. Temperature runs up to 105° or 106°. White blood corpuscles 9,000. Hæmoglobin 75%. Numerous Benign Tertian parasites in the blood. A typical case of Tertian fever seen on the 10th day of the disease. Ten grains of "Laverain" were given on the 13th day, ten grains on the 14th day, and ten grains on the 15th day. The first dose was not in time to prevent the attack of fever of the 14th day, but after that no fever occurred, nor has any occurred since that time. The patient's fever was promptly reduced by "Laverain" but as a precautionary measure she continued to take it, though in smaller doses, for two weeks.

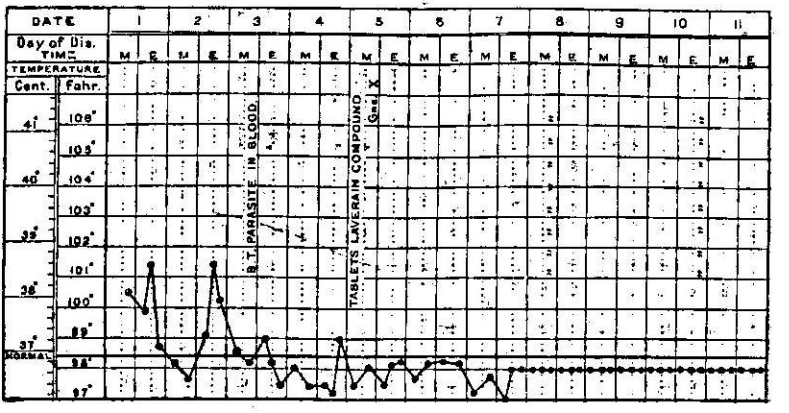


CHART II. "Laverain."

Case II.—Narayan, Hindu. (Chart II). Complains of fever of 10 days' duration, headache, and constipation. The fever came on with a rigor and a chill. The spleen was palpable below the costal margin and the liver enlarged. *Benign Tertian parasites* were found in the blood. Five "Laverain" Tablets were given on the 13th day, and again on succeeding days. The result was immediate, the temperature not rising again above 99° and that only on the 14th day; there was no relapse.

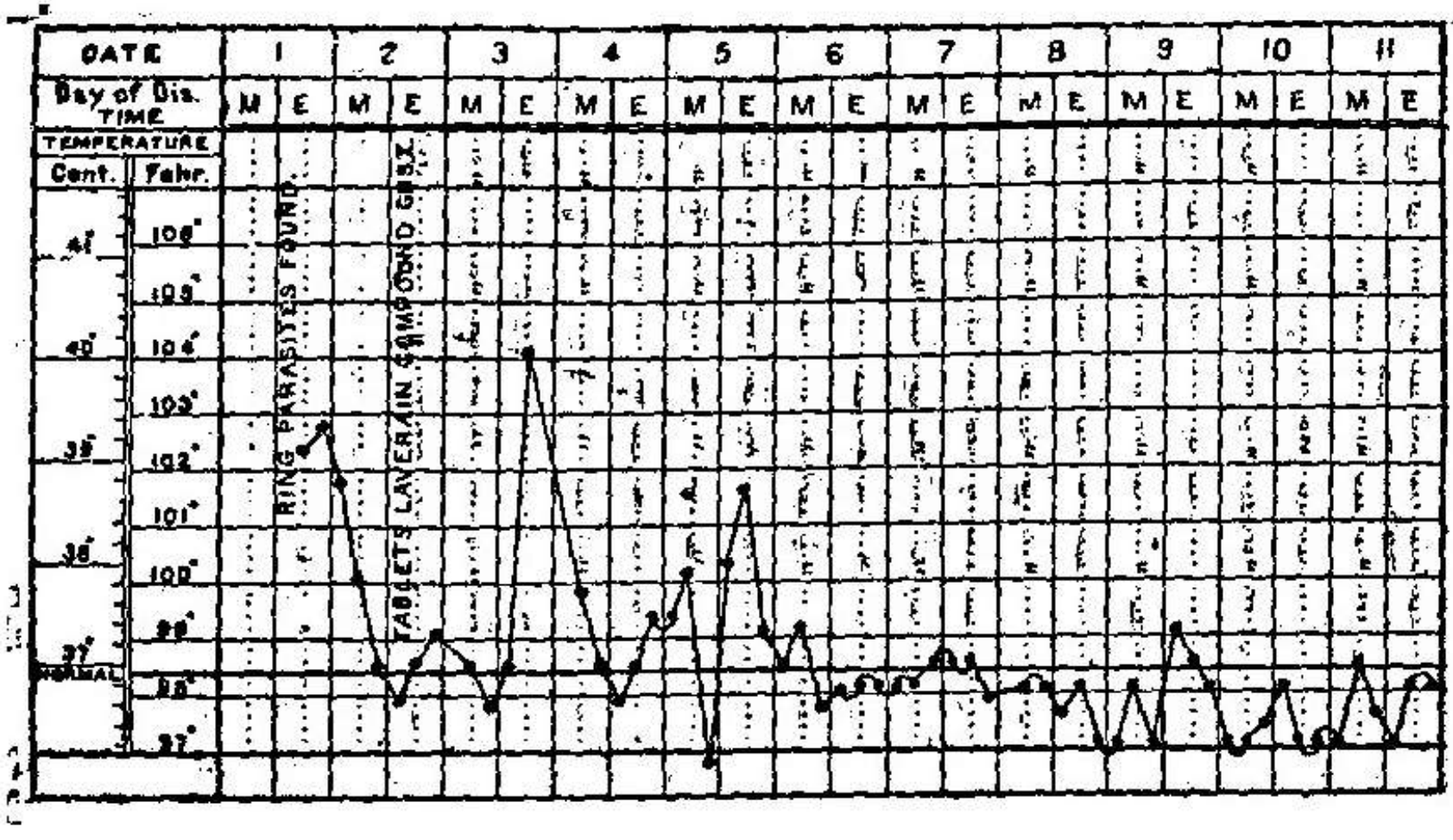


CHART III. "Laverain."

Case III.—J. A. F., a railway guard. (Chart III.) Fever for 20 days. Suffered from Malarial fever in 1904. Exposed to rain and was attacked with fever. Came to hospital on the 21st day. Spleen enlarged, rigor, vomiting, liver congested. Young Malignant Tertian parasites. "Laverain" given (grs. x) on the 22nd day. Fever as usual on the 23rd and 25th days, after that no rise of temperature and no relapse.

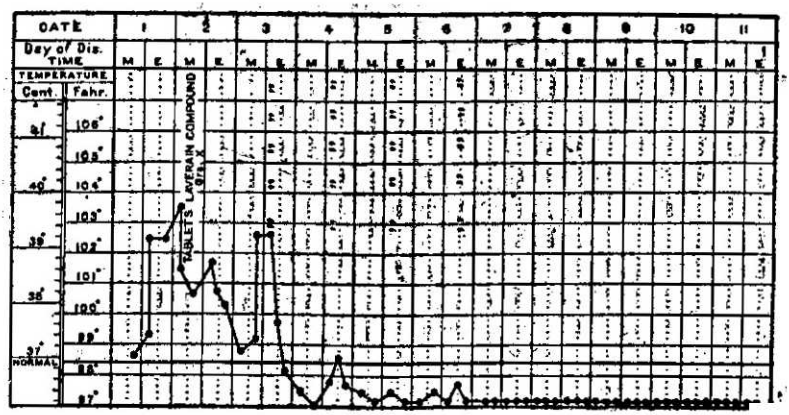


CHART IV. "Laverain."

Case IV.—Mrs. J. D. (Chart IV), inhabitant of Howrah, admitted for high fever of 10 days' duration and enlarged spleen. Says that 10 days ago she had a severe rigor and that this was followed by high fever. Liver tender and slightly enlarged. Patient is anæmic. Spleen enlarged and tender. *Malignant Tertian Parasites and Crescents in the blood.* "Laverain" Tablets, grs. x, on the 12th day, but not in time to abort the attack of the 13th day. After that however there was no fever nor any relapse whilst in hospital (20 days).

I have detailed above two cases each of Benign and Malignant Tertian in which the parasite was found in the blood. I give next a case in which no parasite was found, but where the clinical test and history made the diagnosis quite certain.

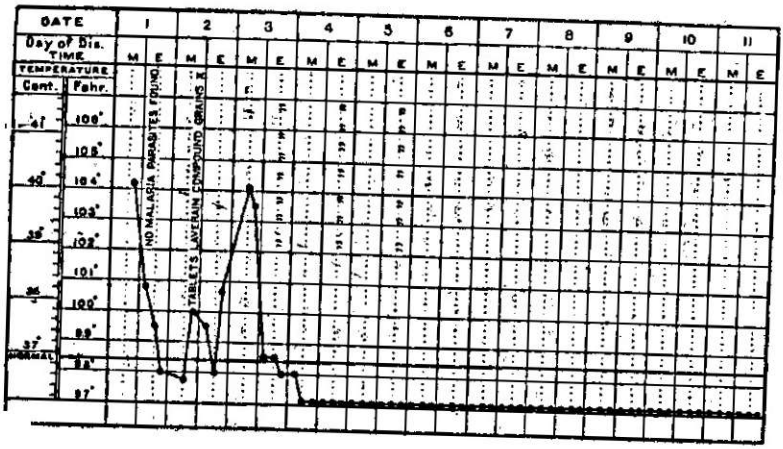


CHART V. "Laverain."

Case V.—Anamula, aged 20 years. (Chart V.) Complains of fever for two months. This occurs in the morning with rigor and headache.

Is employed at Serampore. Gets fever regularly at 11 A.M. daily and this remains till 4 P.M. This has gone on for two months without ceasing. There is jaundice, liver is tender, with constipation and anorexia. The spleen is 2½ inches below the costal-margin. The red cells are 1,700,000, the white cells 3,225.

"Laverain," grs. X, was given on the day after admission, there was fever the next day and then no more throughout the patient's stay in hospital, although according to her statement it had persisted for 2 months previous to admission.

The above five cases are merely examples of many others which have been treated in my wards. At the time of writing (November) cases of Malaria are still being admitted so that the records for the year cannot be made up. The cases quoted will serve to show the efficacy of "Laverain" in the Benign and Malignant Tertian fevers.

Unfortunately, I have had so far this year no undoubted Quartan case, with which to test the drug.

Suggested method of treatment.

Recent researches have shewn the importance of early and effectual treatment of Malaria so that the young parasites may be killed off before they have an opportunity of becoming immune to Quinine or its derivatives.

As a matter of practice, ten grains or less of "Laverain" given daily for three days will, in that period, bring any case of Malarial fever to normal, or at any rate make a very marked impression on it.

I usually administer a purge of Calomel 5 grs. with Bicarbonate of Soda 10 grs. followed by a saline—in fact in ordinary dispensary practice the White mixture or saline is used to wash down the Calomel and is given by the Medical Officer in the consulting room. I regard this *preliminary treatment* as *of the greatest importance.*

Following this the patient receives ten grains of "Laverain" daily for the first seven days, six grains daily for the next seven days, and finally ten grains in two successive days for as many weeks as practicable.

It is immaterial how the "Laverain" is given; it may be before or after food, just in the ordinary hospital routine.

I generally use five 2 gr. tablets and distribute them over the day, but any other method of administration would probably be effectual.

If the object be simply to reduce the fever it is not necessary to use the "Laverain" for such a long period, but for the prevention of relapses a prolonged administration is desirable.

Note by Smith, Stanistreet & Co.

A consideration of the steadily increasing price of Quinine, which has advanced 30% during the past 18 months and will probably advance still higher during the next year, will shew that an immense saving in expenditure on Quinine or on Quinine Tablets can be made by the substitution of "Laverain," with better results than is now obtainable by the use of either the Quinine Sulphate or Hydrochloride.

As a matter of fact, "Laverain" Tablets are supplied at practically half the price of 5 grain Quinine Tablets, and roughly 10 grains of "Laverain" is equivalent in efficacy to 25 grains of Quinine Sulphate. Each "Laverain" Tablet may therefore be taken as the equivalent of one 5 grain Quinine Tablet, the price being exactly half.

To large employers of native labour, who systematically dose their coolies with Quinine, the use of "Laverain" Tablets thus offers a saving of not less than 50% in cost, besides giving more uniformly effective protection against Malaria.

"Laverain" Tablets are put up in screw capped bottles containing 1,000, price Rs. 8 per thousand, or in quantities of 20,000 or more at Rs. 7-8 per thousand. They are also supplied in bottles of 100 and of 25 at correspondingly increased prices. We shall be glad to send a sample bottle free of charge, to any medical man who sends us his name and address with a request for trial sample.

Price of the 1000 size is advanced to 10/-

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